Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	10320	sarcosine or (methylamino adj (acetic or ethanoic) adj acid) methylglycine sarcosin or (sarcosinic adj acid)	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:46
L2	3684	dimethylglycine or ((aminoisobutanoic or aminoisobutyric) adj acid)	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:48
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L9	1971	I1 and I4	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:52
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L11	1442	I1 and I3	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:52
L12	146	l11 and l4 and l5	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:52
L13	1325	l11 and l6	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:52
L14	555	113 and 17 and 18	US-PGPUB; USPAT	OR	OFF	2006/04/12 17:54
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			USPAT			
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			·	·	I	T
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L61	37	l60 and betaine	USPAT	OR	OFF	2006/04/12 18:49
L62	118	betaine and dimethylglycine	USPAT	OR	OFF	2006/04/12 18:49

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L63	118	betaine and dimethylglycine	USPAT	OR	OFF	2006/04/12 18:49
L64	34	l63 and sarcosine	USPAT	OR	OFF	2006/04/12 18:50
L65	. 1	"5464619".pn.	US-PGPUB; USPAT	OR	OFF	2006/04/12 19:24
L66	146	(dehydration or hypotonic or rehydration or hydration?) and (taurine and citrate)	USPAT	OR	OFF	2006/04/12 19:28
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L73	79	l71 and carbohydrate	USPAT	OR	OFF	2006/04/12 20:07
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- Introduction to Carbohydrates
- Carbohydrate Nomenclature
- Monosaccharides
- Disaccharides
- Polysaccharides
- Glycogen
- Starch

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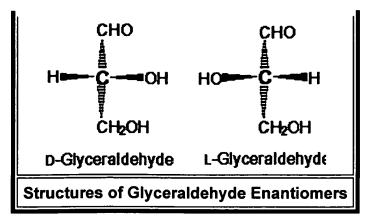
Introduction

Carbohydrates are carbon compounds that contain large quantities of hydroxyl groups. The simplest carbohydrates also contain either an aldehyde moiety (these are termed polyhydroxyaldehydes) or a ketone moiety (polyhydroxyketones). All carbohydrates can be classified as either monosaccharides, oligosaccharides or polysaccharides. Anywhere from two to ten monosaccharide units, linked by glycosidic bonds, make up an oligosaccharide. Polysaccharides are much larger, containing hundreds of monosaccharide units. The presence of the hydroxyl groups allows carbohydrates to interact with the aqueous environment and to participate in hydrogen bonding, both within and between chains. Derivatives of the carbohydrates can contain nitrogens, phosphates and sulfur compounds. Carbohydrates also can combine with lipid to form glycolipids or with protein to form glycoproteins. back to the top

Carbohydrate Nomenclature

The predominant carbohydrates encountered in the body are structurally related to the aldotriose glyceraldehyde and to the ketotriose dihydroxyacetone. All carbohydrates contain at least one asymmetrical (chiral) carbon and are, therefore, optically active. In addition, carbohydrates can exist in either of two conformations, as determined by the orientation of the hydroxyl group about the asymmetric carbon farthest from the carbonyl. With a few exceptions, those carbohydrates that are of physiological significance exist in the D-conformation. The mirror-image conformations, called enantiomers, are in the L-conformation.





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Monosaccharides

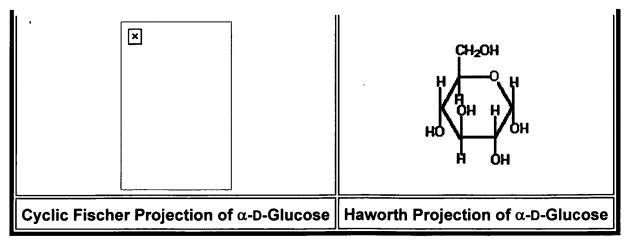
The monosaccharides commonly found in humans are classified according to the number of carbons they contain in their backbone structures. The major monosaccharides contain four to six carbon atoms.

Carbohydrate Classifications

# Carbons	Category Name	Relevant examples				
3	Triose	Glyceraldehyde, Dihydroxyacetone				
4	Tetrose	Erythrose				
5	Pentose	Ribose, Ribulose, Xylulose				
6	Hexose	Glucose, Galactose, Mannose , Fructose				
7	Heptose	Sedoheptulose				
9	Nonose	Neuraminic acid also called sialic acid				

The aldehyde and ketone moieties of the carbohydrates with five and six carbons will spontaneously react with alcohol groups present in neighboring carbons to produce intramolecular hemiacetals or hemiketals, respectively. This results in the formation of five- or six-membered rings. Because the five-membered ring structure resembles the organic molecule furan, derivatives with this structure are termed furanoses. Those with six-membered rings resemble the organic molecule pyran and are termed pyranoses.

Such structures can be depicted by either Fischer or Haworth style diagrams. The numbering of the carbons in carbohydrates proceeds from the carbonyl carbon, for aldoses, or the carbon nearest the carbonyl, for ketoses.



The rings can open and re-close, allowing rotation to occur about the carbon bearing the reactive carbonyl yielding two distinct configurations (α and β) of the hemiacetals and hemiketals. The carbon about which this rotation occurs is the anomeric carbon and the two forms are termed anomers. Carbohydrates can change spontaneously between the α and β configurations— a process known as mutarotation. When drawn in the Fischer projection, the α configuration places the hydroxyl attached to the anomeric carbon to the right, towards the ring. When drawn in the Haworth projection, the α configuration places the hydroxyl downward.

The spatial relationships of the atoms of the furanose and pyranose ring structures are more correctly described by the two conformations identified as the chair form and the boat form. The chair form is the more stable of the two. Constituents of the ring that project above or below the plane of the ring are axial and those that project parallel to the plane are equatorial. In the chair conformation, the orientation of the hydroxyl group about the anomeric carbon of α -D-glucose is axial and equatorial in β -D-glucose.

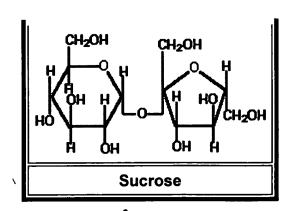
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Disaccharides

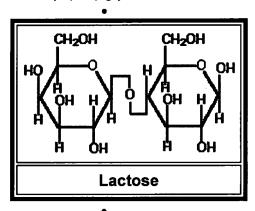
Covalent bonds between the anomeric hydroxyl of a cyclic sugar and the hydroxyl of a second sugar (or another alcohol containing compound) are termed glycosidic bonds, and the resultant molecules are glycosides. The linkage of two monosaccharides to form disaccharides involves a glycosidic bond. Several physiogically important disaccharides are sucrose, lactose and maltose.

• **Sucrose**: prevalent in sugar cane and sugar beets, is composed of glucose and fructose through an α -(1,2) β -glycosidic bond.

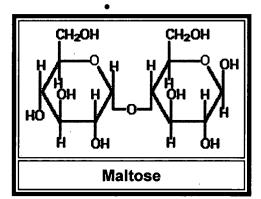




• Lactose: is found exclusively in the milk of mammals and consists of galactose and glucose in a β -(1,4) glycosidic bond.



• **Maltose**: the major degradation product of starch, is composed of 2 glucose monomers in an α -(1,4) glycosidic bond.



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Polysaccharides

Most of the carbohydrates found in nature occur in the form of high molecular weight polymers called polysaccharides. The monomeric building blocks used to generate polysaccharides can be varied; in all cases, however, the predominant **monosaccharide** found in polysaccharides is D-glucose. When polysaccharides are composed of a single **monosaccharide** building block, they are termed homopolysaccharides. Polysaccharides composed of more than one type of **monosaccharide** are termed heteropolysaccharides. back to the top

Glycogen

Glycogen is the major form of stored carbohydrate in animals. This crucial molecule is a homopolymer of glucose in α -(1,4) linkage; it is also highly branched, with α -(1,6) branch linkages

occurring every 8-10 residues. Glycogen is a very compact structure that results from the coiling of the polymer chains. This compactness allows large amounts of carbon energy to be stored in a small volume, with little effect on cellular osmolarity. back to the top

Starch

Starch is the major form of stored carbohydrate in plant cells. Its structure is identical to glycogen, except for a much lower degree of branching (about every 20-30 residues). Unbranched starch is called **amylose**; branched starch is called **amylopectin**. back to the top

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Molecular Biochemistry I

Carbohydrates - Sugars and Polysaccharides

Contents of this page:

Introduction to carbohydrates

Monosaccharides: nomenclature, stereochemistry, & cyclic forms

Sugar derivatives

Glycosidic bonds & disaccharides

Polysaccharides - amylose, amylopectin & cellulose

Glycosaminoglycans & proteoglycans

Oligosaccharides of glycoproteins & glycolipids

Lectins

Carbohydrates (also referred to as glycans) have the basic composition:

- Monosaccharides simple sugars, with multiple hydroxyl groups. Based on the number of carbons (e.g., 3, 4, 5, or 6) a monosaccharide is a triose, tetrose, pentose, or hexose, etc.
- Disaccharides two monosaccharides covalently linked
- Oligosaccharides a few monosaccharides covalently linked.
- Polysaccharides polymers consisting of chains of monosaccharide or disaccharide units.

Monosaccharides:

Aldoses (e.g., glucose) have an aldehyde at one end.

Ketoses (e.g., fructose) have a **keto group**, usually at C #2.

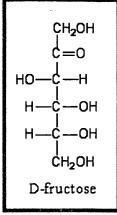
Nomenclature for stereoisomers: D and L designations are based on the configuration about the single asymmetric carbon in glyceraldehyde. (See also Voet & Voet, 3rd Ed, p. 73).

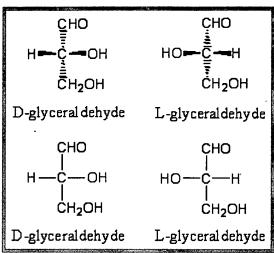
The lower representations are Fischer Projections.

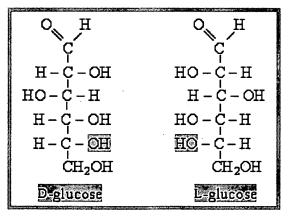
For sugars with more than one chiral center, the **D** or **L** designation refers to the **asymmetric carbon farthest** from the aldehyde or keto group.

Most naturally occurring sugars are D isomers.

D & L sugars are mirror images of one another. They have the same name. For example, D-glucose and L-glucose are shown at right.







Other stereoisomers have unique names, e.g., glucose, mannose, galactose, etc. The number of stereoisomers is 2 ⁿ, where n is the number of asymmetric centers. The six-carbon aldoses have 4 asymmetric centers, and thus 16 stereoisomers (8 D-sugars and 8 L-sugars). See diagrams of D-aldoses in Voet & Voet on p. 357, and D-ketoses on p. 358.

An aldehyde can react with an alcohol to form a hemiacetal.

Similarly a ketone can react with an alcohol to form a hemiketal.

Pentoses and hexoses can **cyclize**, as the aldehyde or keto group reacts with a hydroxyl on one of the distal carbons.

E.g., glucose forms an intra-molecular hemiacetal by reaction of the aldehyde on C1 with the hydroxyl on C5, forming a six-member **pyranose** ring, named after the compound pyran. See also diagrams p. 359.

The representations of the cyclic sugars at right are called **Haworth projections**.

Fructose can form either:

- a six-member **pyranose** ring, by reaction of the C2 keto group with the hydroxyl on C6
- a 5-member furanose ring, by reaction of the C2 keto group with the hydroxyl on C5.

Cyclization of glucose produces a new asymmetric center at C1, with the two stereoisomers called anomers, $\alpha \& \beta$.

Haworth projections represent the cyclic sugars as having essentially planar rings, with the OH at the anomeric C1 extending either:

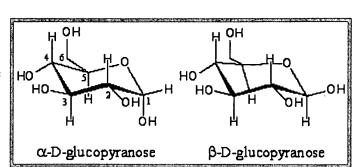
- below the ring (α)
- above the ring (β).

Because of the tetrahedral nature of carbon bonds, the cyclic form of pyranose sugars actually assume a "chair" or "boat" configuration, depending on the sugar (diagrams p. 360).

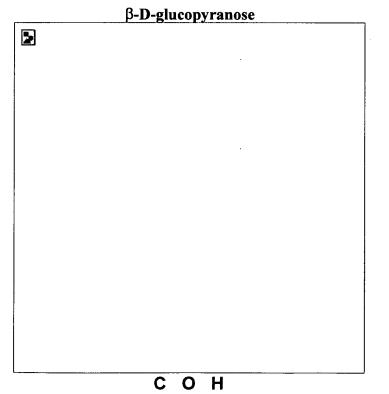
The representation at right reflects the chair configuration of the glucopyranose ring more accurately than the Haworth projection.

The displays below use the <u>Chime</u> plug-in. (These structure files were produced using the program Insight II from Molecular Simulations.)

α-D-glucopyranose



C O H



Click each image, using the right mouse button to change display selections.

Change the display to sticks, to make the image easier to see.

Drag the images, using the left mouse button, to give the 2 structures the same orientation, as in the diagram above. In orienting the molecules, look for the ring O that bridges between C1 and C5, and the OH on C6, which sticks up out of the ring.

Identify & compare the orientation of the OH on C1 of each anomer. If you select atom O1 and change the display to ball & stick, the oxygen atom of the OH on C1 will be more prominent.

Sugar derivatives. Various derivatives of sugars exist (diagrams p. 361-363), including:

Sugar alcohol - lacks an aldehyde or ketone. An example is ribitol.

Sugar acid - the aldehyde at C1, or the hydroxyl on the terminal carbon, is oxidized to a carboxylic acid. Examples are gluconic acid and glucuronic acid.

Amino sugar - an amino group substitutes for one of the hydroxyls. An example is glucosamine. The amino group may be acetylated. At right, the acetic acid moiety is shown in red.

N-acetylneuraminate, (*N*-acetylneuraminic acid, also called **sialic acid**) is often found as a terminal residue of **oligosaccharide** chains of glycoproteins. (See also p. 363.) Sialic acid imparts **negative charge** to glycoproteins, because its carboxyl group tends to dissociate a proton at physiological pH, as shown here.

Glycosidic bonds: The anomeric hydroxyl group and a hydroxyl group of another sugar or some other compound can join together, splitting out water to form a glycosidic bond.

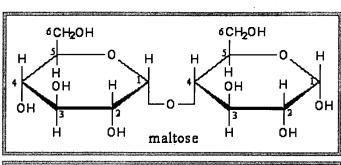
For example, methanol reacts with the anomeric hydroxyl on glucose to form **methyl glucoside** (methylglucopyranose).

$$H_2O$$
 H_2O
 H_2O
 H_3
 G -D-glucopyranose methanol methyl- α -D-glucopyranose

Disaccharides:

Maltose, a cleavage product of starch (e.g., <u>amylose</u>, see below), is a disaccharide with an $\alpha(1\rightarrow 4)$ glycosidic linkage between the C1 hydroxyl of one glucose and the C4 hydroxyl of a second glucose. Maltose is the α anomer, because the O at C1 points down from the ring.

Cellobiose, a product of cellulose breakdown, is the otherwise equivalent β anomer. The configuration at the anomeric C1 is β (O points up from the ring). The $\beta(1\rightarrow 4)$ glycosidic linkage is represented as a "zig-zag" line, but one glucose residue is actually flipped over relative to the other. (See Chime view of cellulose below.)



Other disaccharides include (diagrams p. 364):

- Sucrose, common table sugar, has a glycosidic bond linking the anomeric hydroxyls of glucose and fructose. Because the configuration at the anomeric carbon of glucose is α (O points down from the ring), the linkage is designated $\alpha(1\rightarrow 2)$. The full name is α -D-glucopyranosyl- $(1\rightarrow 2)\beta$ -D- fructopyranose.
- Lactose, milk sugar, is composed of glucose and galactose with $\beta(1\rightarrow 4)$ linkage from the anomeric hydroxyl of galactose. Its full name is β -D-galactopyranosyl- $(1\rightarrow 4)$ - α -D-glucopyranose.

Polysaccharides:

Plants store glucose as amylose or amylopectin, glucose polymers collectively called starch. Glucose storage in polymeric form minimizes osmotic effects.

Amylose is a glucose polymer with $\alpha(1\rightarrow 4)$ glycosidic linkages, as represented above (see also diagram p. 366). The end of the **polysaccharide** with an anomeric carbon (C1) that is not involved in a glycosidic bond is called the

reducing end.

Amylose adopts a helical conformation, as is apparent in the structure at right, viewable by Chime. (This data file was produced using Chem 3D, with MM2 energy minimization.)

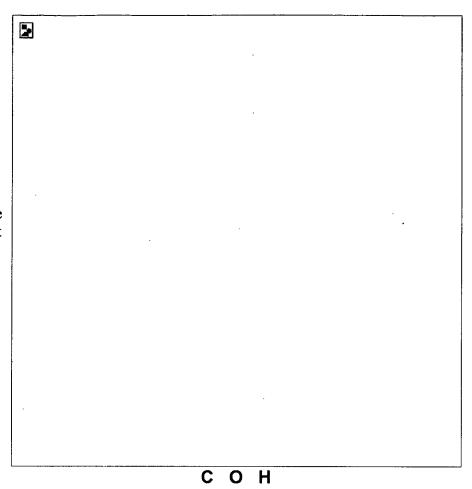
Display as **sticks**, and drag the image. Note the helical structure and the orientation of adjacent glucose residues.

Compare to the diagram above. Look for the - CH₂OH at C6, that sticks up out of each

pyranose ring.

Try other displays.

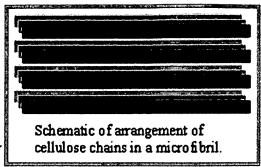
You can make the O atoms more prominent by selecting atom O, and changing the display to ball & stick.



Amylopectin is a glucose polymer with mainly $\alpha(1\rightarrow 4)$ linkages, but it also has branches formed by $\alpha(1\rightarrow 6)$ linkages. The branches are generally longer than shown above. The branches produce a compact structure, and provide multiple chain ends at which enzymatic cleavage of the polymer can occur.

Glycogen, the glucose storage polymer in animals, is similar in structure to amylopectin. But glycogen has more α (1 \rightarrow 6) branches. See the structure of amylopectin above and diagrams on p. 367. The highly branched structure permits rapid release of glucose from glycogen stores, e.g., in muscle cells during exercise. The ability to rapidly mobilize glucose is more essential to animals than to plants.

Cellulose, a major constituent of plant cell walls, consists of long linear chains of glucose, with $\beta(1\rightarrow 4)$ linkages. Every other glucose in cellulose is flipped over, due to the β linkages. This promotes intrachain and interchain hydrogen bonds, as well as van der Waals interactions, that cause cellulose chains to be straight and rigid, and pack with a crystalline arrangement in thick bundles called microfibrils. The regular packing of cellulose strands within a microfibril, stabilized by lateral and above/below strand interactions, is schematically represented at right. See also diagrams in the Voet & Voet text p. 365, and in the Botany online website.



Multisubunit Cellulose Synthase complexes in the plasma membrane spin out from the cell surface microfibrils consisting of 36 parallel, interacting cellulose chains. These microfibrils are very strong. The role of cellulose is to impart strength and rigidity to plant cell walls, which can withstand high hydrostatic pressure gradients. Osmotic swelling is prevented.

A short glucose polymer, equivalent to **cellulose** with $\beta(1\rightarrow 4)$ linkages, may be viewed by Chime below right. In cellulose the strand would straighter, due to interactions between adjacent strands in the cellulose fiber bundle.

-

Display as sticks and drag the image. Note how each glucose residue is flipped over relative to adjacent residues, due to the $\beta(1\rightarrow 4)$ linkages. To orient yourself, look for the ring oxygen of each residue, as well as the -CH₂OH at C6, which sticks up out of each pyranose ring. (See diagram above.) You can make the O atoms prominent by selecting atom O, and changing the display to

(This data file was produced using Chem 3D, with MM2 energy minimization.)

ball & stick.

ow oo s. of ee o M2

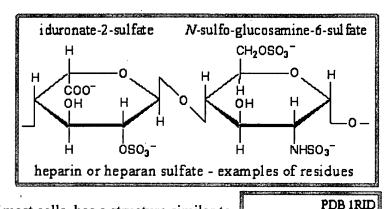
Glycosaminoglycans (mucopolysaccharides) are polymers of

repeating disaccharides (diagrams p. 368-369). Within the disaccharides, the sugars tend to be modified, with acidic groups, amino groups, sulfated hydroxyl and amino groups, etc. Glycosaminoglycans tend to be negatively charged, because of the prevalence of acidic groups.

Hyaluronate is a glycosaminoglycan with a repeating disaccharide consisting of two glucose derivatives, glucuronate (glucuronic acid) and N-acetylglucosamine. The glycosidic linkages are $\beta(1\rightarrow 3)$ and $\beta(1\rightarrow 4)$.

Proteoglycans are glycosaminoglycans that are covalently linked to specific **core proteins**. Some proteoglycans of the extracellular matrix in turn link non-covalently to hyaluronate via protein domains called **link modules**. For example, in cartilage multiple copies of the **aggrecan** proteoglycan bind to an extended hyaluronate backbone to form a large complex (diagrams & micrograph p. 371). **Versican**, another proteoglycan that binds to hyaluronate, is in the extracellular matrix of loose connective tissues. See web sites on aggrecan and aggrecan plus versican.

Heparan sulfate is initially synthesized on a membraneembedded core protein as a polymer of alternating glucuronate and N-acetylglucosamine residues. Later, in segments of the polymer, glucuronate residues may be converted to the sulfated sugar iduronic acid, while Nacetylglucosamine residues may be deacetylated and/or sulfated.



Heparin, a soluble glycosaminoglycan found in granules of mast cells, has a structure similar to that of heparan sulfates, but is relatively highly sulfated. When released into the blood, it inhibits clot formation by interacting with the protein antithrombin. Heparin has an extended helical conformation. Charge repulsion by the many negatively charged groups may contribute to this conformation.

The heparin molecule depicted at right includes 10 residues, alternating IDS (iduronate-2-sulfate) and SGN (*N*-sulfo-glucosamine-6-sulfate).

Color key: C O N S

heparin: (IDS-SGN)₅

, heparan sulfate

glycosaminoglycan

Some cell surface heparan sulfate glycosaminoglycans remain covalently linked to core proteins embedded in the plasma membrane. Proteins involved in signaling and adhesion at the cell surface recognize and bind segments of heparan sulfate chains having particular patterns of sulfation.

Oligosaccharides of glycoproteins and glycolipids: Oligosaccharides that are covalently attached to proteins or to membrane lipids may be linear or branched chains. They often include modified sugars, e.g., acetylglucosamine,

œ-helix

core _

protein

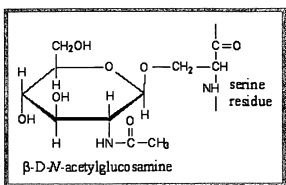
O-linked oligosaccharide chains of glycoproteins vary in complexity.

etc.

They link to a protein via a glycosidic bond between a sugar residue and a serine or threonine hydroxyl (diagram p. 376).

O-linked oligosaccharides have roles in recognition, interaction. (See discussion of lectins below.)

N-acetylglucosamine (abbreviated GlcNAc) is a common O-linked glycosylation of protein serine or threonine residues. Many cellular proteins, including enzymes and transcription factors, are regulated by reversible attachment of GlcNAc. Often attachment of GlcNAc to a protein hydroxyl group alternates with phosphorylation, with these two modifications having opposite regulatory effects (stimulation or inhibition).

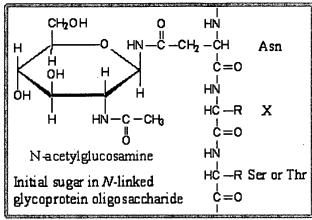


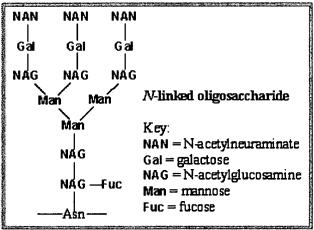
N-linked oligosaccharides of glycoproteins tend to be complex and branched.

Initally *N*-acetylglucosamine is linked to a protein via the side-chain N of an asparagine residue in a particular 3-amino acid sequence.

Additional monosaccharides are added, and the *N*-linked **oligosaccharide** chain is modified by removal and addition of residues, to yield a characteristic branched structure, as at right. (See also p. 376).

Many proteins secreted by cells have attached N-linked **oligosaccharide** chains. Genetic diseases have been attributed to deficiency of particular enzymes involved in synthesizing or modifying **oligosaccharide** chains of these glycoproteins. Such diseases, and gene knockout studies in mice, have been used to define pathways of modification of **oligosaccharide** chains of glycoproteins and glycolipids.

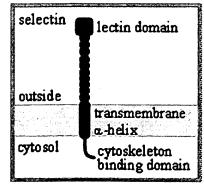




Carbohydrate chains of plasma membrane glycoproteins and glycolipids usually face the outside of the cell. They have roles in cell-cell interaction and signaling, and in forming a protective layer on the surface of some cells.

Lectins are glycoproteins that recognize and bind to specific oligosaccharides. A few examples:

- Concanavalin A and wheat germ agglutinin are plant lectins that have been useful research tools (discussed p. 363).
- Mannan-binding lectin (MBL) is a glycoprotein found in blood plasma. It associates with cell surface carbohydrates of disease-causing microorganisms, promoting phagocytosis of these organisms as part of the immune response.
- Selectins are integral proteins of mammalian cell plasma membranes with roles in cell-cell recognition and binding. A lectin-like domain is at the end of an extracellular segment that extends outward from the cell surface. A cleavage site just outside the transmembrane α-helix provides a mechanism for regulated release



of some lectins from the cell surface. A cytosolic domain participates in regulated interaction with the actin cytoskeleton.

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Additional material on Carbohydrates: Readings, Test Questions, & Tutorial







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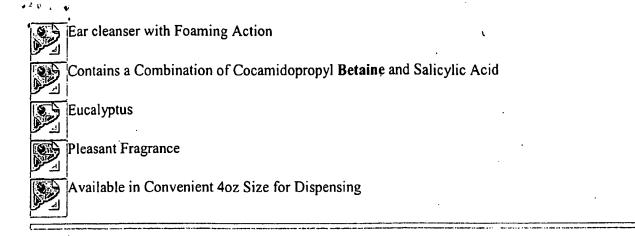


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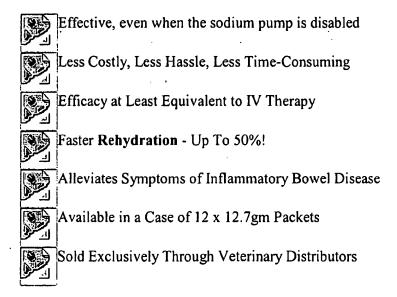
OtiFoam® Ear Cleanser



New From Bio-Nutition Laboratories, LLC (makers of ExClude)

PediaSorb SATM Enteric

A Better Choice For Diarrhea and a New Alternative for Rehydration



Discussion: PediaSorbTM Enteric has demonstrated efficacy when used to rehydrate puppies afflicted with parvovirus and when used for symptomatic control of diarrhea caused by inflammatory bowel disease. It was developed to offer an alternative to cumbersome, costly and time-consuming IV rehydration techniques. The unique formulation of PediaSorbTM Enteric provides efficacy at least equivalent to intravenous fluid replacement, but with much faster rehydration -- up to 50% faster! Intestinal villi are damaged and the sodium pump is often disabled with enteric diseases. Traditional oral electrolytes that contain dextrose as their primary ingredient require healthy villi for absorption. That's why they are often not very effective and explains why veterinarians have preferred intravenous techniques for rehydration. PediaSorbTM Enteric contains several novel ingredients that provide a co-transport system for fluids and electrolytes even in the presence of severely damaged intestinal villi: L-glutamine is a plasma amino acid shown in many human studies to speed regereratino of damaged intestinal villi and to enhance absorbtion of electrolytes and fluids. Complex carbohydrates Maltodextrin and trace protein Hydrolysate provide the same absorption function of glucose but without the need for healthy villi. The co-transport system results in a reversal of diarrhea, instead of just replacing lost fluids as intravenous therapy does. The use of protein hydrolysates in PediaSorbTM Enteric are important

for several reasons: The smaller protein size (less than 1400 Daltons) means better absorption with more complete digestion. These proteins will not cause reactions in dogs or cats with food intolerance, a common condition in animals with inflammatory bowel disease. PediaSorbTM Enteric provides nutritional support for patients that are not eating.

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     Entered STN: 16 Nov 1984
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                                     (CA INDEX NAME)
CN
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CN
     α-Aminoisobutanoic acid
CN
     \alpha-Aminoisobutyric acid
     \alpha-Methylalanine
CN
CN
     2,2-Dimethylglycine
CN
     2-Amino-2-methylpropanoic acid
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82 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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CN
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CN
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     Betafin BP
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     Cystadane
     FinnStim
CN
     Glycine betaine
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     Glycocoll betaine
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     Greenstim
     Loramine AMB 13
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     Anon BL
     Anon BL-SF
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CN
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CN
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     DDN
CN
     Desimex i
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     Dimethyllaurylbetaine
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     Empigen BB/L
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     Genagen LAB
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CN

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Quartholite

● C1-

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70 REFERENCES IN FILE CAPLUS (1907 TO DATE)

16 REFERENCES IN FILE CAOLD (PRIOR TO 1967)